Exhibit 3

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Two-year results from ENDEAVOR III point to safety, efficacy

April 4, 2007 | Shelley Wood

ACC news **New Orleans, LA** - Two-year follow-up from the **ENDEAVOR III** trial suggests that the Endeavor zotarolimus-eluting stent may be equivalent to the sirolimus-eluting Cypher stent, in terms of clinical end points. Rates of major adverse cardiac events (MACE) and target lesion revascularizations (TLR) at two years were not statistically different for the two drug-eluting stents (DES), although fewer patients randomized to the Endeavor experienced periprocedural non-Q-wave MI, a difference that was maintained over the two years of follow-up.

Dr Martin Leon (Columbia University, New York) presented the two-year results during the **American College of Cardiology 2007 Scientific Sessions** last week.

The two-year results are relatively good news for a stent program that appeared poised for a rocky ride when the trial results were first unveiled at the prespecified eight-month follow-up. As reported by **heartwire**, the Endeavor failed to achieve its primary end point of noninferiority for in-segment late lumen loss at eight months when compared with the Cypher, although clinical and angiographic outcomes were more or less equivalent. At the time, these results were reported by co-primary investigator for the trial, **Dr David Kandzari**, who has since left academia for Cordis/Johnson & Johnson.

The ENDEAVOR III late results come during a sea change in the DES arena, where the focus has shifted from a fixation on late loss to concerns over stent thrombosis and associated deaths and MI. In the early days of DES trials, minimal or no late loss was held up as the new gold standard. As a result, the eight-month in-stent late loss in ENDEAVOR III for the Endeavor stent, at 0.62 mm as compared with the Cypher at 0.15 mm ($p<0.001$), and in-segment, at 0.36 mm vs 0.13 mm ($p<0.001$), led to gloomy speculation about the Endeavor stent's future.

"The original study was meant to have a primary surrogate angiographic end point, and it failed to meet that end point," Leon told **heartwire**. "But the trial, of course, was planned many, many years ago, before anybody knew that the late loss would be as high as it was with the Endeavor stent, but at the same time before anybody knew that with a late loss of 0.6 mm you could still have TLR in the mid-single-digit numbers. I think we're still learning about the relationship between TLR and in-stent late loss."

Small sample size

The only statistically significant difference between the two groups at 24 months was in MI rates, all periprocedural non-Q-wave MIs, at 0.6% in the Endeavor-treated patients and 3.6% in Cypher-treated patients ($p=0.04$), a difference that might have been explained by the manner in which events were measured in the trial.

"We don't know exactly why, in this study, the non-Q-wave MI rates were so low," Leon said. "It could be there was less side-branch occlusion, which is something people have hypothesized based on the geometry of the stent design itself. Also, the polymer is very thin—less than 5 µm in total thickness, which means it's almost a quarter of the thickness of the Taxus polymer and less than half the thickness of the Cypher polymer. And it may be that the polymer in and of itself caused less in the way of platelet adhesion, side-branch occlusion, we don't know for sure. You can also argue that this was a relatively small study and sometimes you see statistical significance that may be not biologically meaningful, but just due to the large confidence intervals of a small sample size."

Small sample size could also be scrutinized for other end points. While differences in TLR rates between the two stents were not statistically significant, numerically TLRs were greater in the Endeavor stent-treated patients, while deaths were numerically lower.

ENDEAVOR III: Clinical events at two years

Event	Endeavor, n=313 (%)	Cypher, n=112 (%)	p
All death	1.6	4.5	0.14
Q-wave MI	0	0	—
Non-Q-wave MI	0.6	3.6	0.04
Stent thrombosis	0	0	—
TLR	7.0	4.5	0.50
MACE	9.3	11.6	0.47

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Leon told **heart*wire*** that the two-year results from ENDEAVOR III alone do not add much to the stent-thrombosis debate, since rates of stent thrombosis per the trial's definition were zero between both stents. However, in an analysis of all the Endeavor stent data out to two years—more than 1300 patients—there have been no reported stent thromboses, he said.

"Now we're beginning to achieve a large-enough sample size where our confidence about late stent thrombosis is increasing," he said "It's by no means definitive: I'm anxious to see three-year follow-up from **ENDEAVOR II** and whether these results continue to sustain themselves. But if we don't see significant late stent thrombosis at three years, then I think people will feel more confident that among the DES currently available—the Cypher or Taxus—this appears to have a better safety profile."

The end of surrogate outcomes

At the very least, the two-year ENDEAVOR III results add muscle to the push to exclude surrogate outcomes from primary end points in DES trials.

"I think a lot of people—me included—were a little bit naive," Leon said. "When we heard the **RAVEL** results, with no late loss and zero restenosis, everyone was ecstatic. But I think we learned since then that probably that degree of late loss reduction does impair healing sufficiently, and it may induce some negative biologic consequences. So I think that people are willing to concede that a somewhat higher late loss is acceptable."

Whether accepting some late loss truly leads to improved safety without sacrificing meaningful reductions in TLR remains to be seen. Three-year results for ENDEAVOR II will be reported at the **EuroPCR** meeting in May, he noted. Nine-month clinical and eight-month angiographic results from **ENDEAVOR IV**, with the Taxus stent as the comparator in 1500 patients, are to be presented at **TCT 2007**.

Related links

Late lumen loss a problem once again for the new Endeavor stent
[*HeartWire* > *Interventional cardiology*; Oct 17, 2005]

Late loss in ENDEAVOR II dampens enthusiasm, despite improved clinical, anglographic outcomes over bare stent
[*HeartWire* > *Interventional cardiology*; Mar 07, 2005]

Fears of catch-up phenomenon mar otherwise positive 12-month results for ENDEAVOR I
[*HeartWire* > *Other News*; May 25, 2004]